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The Number of Lymph Node Metastases Influences Survival in Esophageal Cancer

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Background and Objectives: Lymph node involvement adversely affects the survival of patients with esophageal cancer. We retrospectively investigated whether the number of involved lymph nodes and the degree of lymph node dissection affect survival.

Patients and Methods: Eighty-eight patients underwent surgical resection and reconstruction for T1–T3 thoracic esophageal squamous cell carcinoma. Patients were classified into three groups: group 1, 32 patients without lymph node involvement; group 2, 26 patients with 1 to 3 positive nodes; and group 3, 30 patients with ≧4 involved lymph nodes.

Results: The 3-year and 5-year survival rates were 34.8% and 30.0% in group 1, 30.0% and 22.7% in group 2, and 14.8% and 0% in group 3, respectively. The mean survival time (MST) X ±SD of the patients in group 3 (453.06 ± 74.5 days) was significantly shorter than in group 1 (450.1 ± 450.5, $P = 0.0005$) and group 2 (937.3 ± 1317.9, $P = 0.0295$). For patients in groups 1 and 2, the MST for three-field lymph node dissection (1136.9 ± 1476.4 days) was longer than for two-field lymph node dissection (1007.4 ± 1476.4 days, $P = 0.0355$). However, in group 3, there was no survival advantage to three-field lymph node dissection.

Conclusion: We conclude that the survival in patients with thoracic esophageal cancer involving four or more nodes, is poorer than in patients with lesser involvement. Three-field lymph node dissection does contribute to prolonged survival in patients with node-negative disease or fewer than four positive nodes.

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KEY WORDS: esophageal cancer; lymph node metastasis; lymph node dissection

INTRODUCTION

Multifactorial analysis of esophageal cancer identified the depth of esophageal wall penetration and lymph node spread as poor prognostic factors [1–3]. Successful lymph node dissection depends on sufficient removal of the lymph node groups that comprise the lymphatic drainage of the tumor. In this study, we retrospectively investigated whether the number of involved lymph nodes and the degree of lymph node dissection affect survival in patients with thoracic esophageal cancer.

PATIENTS AND METHODS

From January 1974 to December 1995, an Ivor Lewis procedure for intraesophageal cancer was performed in 82 patients and a left thoracoabdominal esophagectomy in 6 patients. Forty-four patients underwent dissection of perigastric and mediastinal nodes (two-field dissection), and 44 patients underwent dissection of perigastric, mediastinal, and cervical nodes (three-field dissection). Eighty-eight patients with squamous cell carcinoma of stages T1, T2, or T3, were analyzed for survival. Stage of the disease was according to UICC-TNM classification of esophageal cancer [4]. Patients with T4 or stage IV

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TABLE I. Cancer of the Esophagus: Patient Characteristics

Variable	No. of positive nodes: Group 1 0 (n = 32)	Group 2 ≦3 (n = 26)	Group 3 ≧4 (n = 30)	*P*
Age distribution (years)				
40–49	1	0	2	
50–59	7	11	13	
60–69	15	8	11	
70–79	9	7	4	0.306 (NS)
Gender				
Male	31	25	28	
Female	1	1	2	0.783 (NS)
Primary tumor				
T1	12	1	1	
T2	7	7	4	
T3	13	18	25	0.0007
Tumor location				
Upper	7	2	0	
Middle	18	14	18	
Lower	7	10	12	0.051 (NS)
Operative procedure				
Ivor-Lewis procedure	32	24	29	
Left thoracoabdominal esophagectomy	0	2	2	0.275 (NS)
Lymph node dissection				
Mediastinal and perigastric	17	15	12	
Cervical, mediastinal, and perigastric	15	11	18	0.379 (NS)

disease, adenocarcinoma, or anaplastic carcinoma, and patients who died within 30 days postoperatively, were excluded from this study. Patients who underwent transhiatal esophagectomy were also excluded.

The primary tumor was T1 in 14 patients, T2 in 18 patients, and T3 in 56 patients, located in the upper intrathoracic esophagus in 9 patients, in the middle esophagus in 50 patients, and in the lower intrathoracic or abdominal esophagus in 29 patients.

Patients were classified into three groups: group 1, 32 patients without lymph node involvement; group 2, 26 patients with 1 to 3 involved nodes; and group 3, 30 patients with ≧4 positive nodes.

Patient characteristics are shown in Table I. Except for the primary tumor stage, there was no difference in patient characteristics or disease among patients in the three groups. In T3 disease, lymph node involvement occurred significantly more frequently than in T1 or T2 disease ($P = 0.0007$). Characteristics of the groups were compared using the chi-squared test. Cumulative survival was calculated by the Kaplan-Meier method and compared by the log-rank test. T-factor, number of node metastases, and degree of lymph node dissection were analyzed using Cox's proportional-hazard regression model. *P* values of less than 0.05 were considered significant and were based on two-tailed tests.

RESULTS

The cancer death rate was 46.8% (15/32) in group 1, 76.9% (20/26) in group 2, and 86.7% (26/30) in group 3. The positive lymph node group most distant from the intrathoracic esophageal tumor at surgery is shown in Table II. Eleven patients (42.3%) in group 2 showed extrathoracic node involvement at surgery. In all 30 patients (100%) in group 3, extrathoracic node involvement was identified at surgery. Local recurrence occurred in only two patients (6.3%) in group 1. Hematogenous metastasis and local recurrence occurred more frequently in groups 2 and 3 than in group 1 (Table III).

The overall 3-year survival rate of patients with T1–T3 disease was 34.7% in group 1, 30.0% in group 2, and 14.8% in group 3. The 5-year survival rate was 30.0% in group 1, 22.7% in group 2, and 0% in group 3. The overall mean survival time (MST) of patients with T1–T3 disease was 1169.5 ± 1482.0 days in group 1, 937.3 ± 1317.9 days in group 2, and 450.1 ± 450.5 days in group 3 (Table IV). The MST of patients in group 3 was significantly shorter than in group 1 ($P = 0.0005$) and group 2 ($P = 0.0259$) (Table IV).

The overall 3-year survival rate of patients with T3 disease was 25.0% in group 1, 28.5% in group 2, and 9.0% in group 3. The 5-year survival rate were 28.5% in group 1, 25.0% in group 2, and 0% in group 3. The MST of patients with T3 disease in group 3 (389.3 ± 393.6 days) was significantly shorter than in group 1 (1037.7 ± 1582.6 days, $P = 0.0419$) (Table IV). However, there was no significant difference in MST between groups 1 and 2, and between groups 2 and 3 (Table IV).

Overall 3-year and 5-year survival rates were 17.9% and 12.8%, respectively, in the two-field dissection

TABLE II. Cancer of the Esophagus: Extent of Lymph Node Involvement at Surgery*

Lymph node group	No. of patients (%) Group 2 (n = 26)	Group 3 (n = 30)	*P*
Intrathoracic	12 (46.2)	26 (86.7)	
Parasesophageal	11 (42.3)	23 (76.7)	0.01
Paratracheobronchial	2 (7.7)	16 (53.3)	0.0008
Extrathoracic	16 (61.5)	30 (100)	
Perigastric	15 (57.7)	29 (96.7)	0.001
	(n = 11)	(n = 18)	
Cervical	2 (18.2)	12 (66.7)	0.03

*Group 2, ≦3 positive nodes; group 3, ≧4 positive nodes.

TABLE III. Cancer of the Esophagus: Recurrence Rates

Recurrence	No. of patients (%) Group 1 (n = 32)	Group 2 (n = 26)	Group 3 (n = 30)
Hematogenous	8 (25)	13 (50.0)	9 (30.0)
Lymphogenic	11 (34.4)	3 (11.5)	7 (23.3)
Local	2 (6.3)	10 (38.5)	14 (46.4)

TABLE IV. Mean Survival Time According to the Number of Positive Nodes in Patients With Cancer of the Esophagus

Groups[a]	No. of patients	Mean survival time (days)	*P*
T1–T3 disease			
Group 1	32	1169.5 ± 1482.0	0.183 (NS)
Group 2	26	937.3 ± 1317.9	0.0005
Group 3	30	450.1 ± 450.5	0.02
T1–T2 disease			
Group 1	19	1259.7 ± 1446.3	0.727 (NS)
Group 2	8	848.0 ± 846.3	0.1750 (NS)
Group 3	5	754.0 ± 634.8	0.30 (NS)
T3 disease			
Group 1	13	1037.7 ± 1582.6	0.27 (NS)
Group 2	18	977.1 ± 1501.2	0.0419
Group 3	25	389.3 ± 393.6	0.072 (NS)

[a]Group 1, node-negative disease; group 2, ≦3 positive nodes; group 3, ≧4 positive nodes.
NS, not significant.

group, and 35.4% and 20.0% respectively in the three-field dissection group. Three-year and 5-year survival rates were 22.2% and 18.5% in the two-field group, and 50.0% and 40.0%, respectively, in the three-field group. In patients with node-negative disease or less than four positive nodes, the MST of the three-field dissection group (1136.9 ± 1336.3 days) was longer than that of the two-field dissection group (1067.4 ± 1476.4 days, $P = 0.0355$) (Table V).

DISCUSSION

We have demonstrated that prognosis is poorer in patients with four or more positive nodes. Positive nodes in a completely resected tumor adversely affect survival [1–3]. Thomas et al. [6] reported that resected patients who were node-negative had a median survival of 24 months compared with 14 months for node-positive patients. Abe et al. [5] reported the 5-year survival rate was 50.9% with <1 involved node; survival decreased to 29.8% with >2 positive nodes even when lymph node metastasis was confined to one anatomic compartment. All patients with two positive nodes died within 4 years of surgery, and all with involvement of three or more nodes died within 3 years. The presence of even a small number of involved nodes was deleterious to outcome, even when the main tumor was limited to the esophageal wall [5]. In our study, lymph node involvement was limited within mediastinal nodes in about 60% of the patients with ≦3 positive nodes. Extrathoracic lymph node (cervical or perigastric nodes) involvement was found in all patients with ≧4 positive nodes. The cancer in the patients with ≧4 positive nodes was considered to be extended systemically with surgery, therefore, the survival of the patients with ≧4 positive nodes was poorer than in the patients with ≦3 positive nodes.

The degree of lymph node dissection was another important factor in survival of patients in our study. Sannohe et al. [7] found right supraclavicular node involvement in 26.7% of patients with thoracic esophageal cancer, making three-field dissection of the supraclavicular, intrathoracic, and abdominal perigastric lymph nodes necessary for complete resection. Isono et al. [8] reported that three-field dissection increased patient survival rate; the 5-year survival rate with three-field dissection was 44.2% for 172 patients between 1983 and 1992, up from 26.2% for 183 patients without dissection between 1964 and 1982. Three-field lymph node dissection is indicated for T2, T3, and T4 disease. Three-field lymphadenectomy is also indicated for patients with nodal involvement or cancer in the upper intrathoracic esophagus [8]. In our study, the MST in patients with node-negative disease or three or fewer positive nodes was longer in those receiving three-field dissection than in those receiving two-

TABLE V. Cancer of the Esophagus: Mean Survival Time and Lymph Node Dissection

Node dissection	No. of patients	Mean survival time (days)	*P*
Overall			
Two fields	44	838.5 ± 1297.4	
Three fields	44	872.8 ± 1112.7	0.0761 (NS)
Node-negative			
Two fields	17	1010.2 ± 1443.5	
Three fields	15	1350.1 ± 1554.5	0.1155 (NS)
Node-positive disease (≧1)			
Two fields	29	730.4 ± 1212.5	
Three fields	30	626.4 ± 712.8	0.3206 (NS)
Node-negative or positive disease (0–3)			
Two fields	27	1007.4 ± 1476.4	
Three fields	29	1136.9 ± 1336.3	0.0355
Node-positive disease (1–3)			
Two fields	15	1004.2 ± 1559.5	
Three fields	11	846.1 ± 959.4	0.2844 (NS)
Node-positive disease (≧4)			
Two fields	12	388.1 ± 386.4	
Three fields	18	491.4 ± 495.0	0.2860 (NS)

NS, not significant.

field dissection. However, three-field dissection did not benefit patients with four or more positive nodes.

Skinner [9] suggested a modification of the staging system to separate patients with one to four positive lymph nodes (N1) from those with more than four positive lymph nodes (N2). Thus, stage II esophageal cancer would be divided into stage IIA (T3, N0, M0) and stage IIB (T1–2, N1, M0). All N2 disease would be considered stage III [9]. Our data suggest that the number of involved nodes influences patient survival independently. Thus, T3 with nodal involvement stage III disease (T3N1) may be further classified into two groups according to the number of involved nodes. Multi-institutional studies are needed to confirm whether the number of involved nodes affects survival of patients with esophageal cancer.

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